

10 20 30 40 50 60
 GTTGTGCTG TGGCTGATAG CCCCAGCAGG GCCTGCACCT GTGTCCCACC CCACCCACAG
 70 80 90 100 110 120
 ACGGCCTTCT GCAATTCCGA CCTCGTCATC AGGGCCAAGT TCGTGGGGAC ACCAGAAGTC
 130 140 150 160 170 180
 AACCAGACCA CCTTATACCA GCGTTATGAG ATCAAGATGA CCAAGATGTA TAAAGGGTTC
 190 200 210 220 230 240
 CAAGCCTTAG GGGATGCCGC TGACATCCGG TTCGTCTACA CCCCCGCCAT GGAGAGTGTC
 250 260 270 280 290 300
 TCGCGATACT TCCACAGGTC CCACAACCGC AGCGAGGAGT TTCTCATGTC TGGAAAAGTC
 310 320 330 340 350 360
 CAGGATGGAC TCTTGACAT CACTACCTGC AGTTTCGTGG CTCCCTGGAA CAGCCTGAGC
 370 380 390 400 410 420
 TTAGCTCAGC GCCGGGGCTT CACCAAGACC TACACTGTTG GCTGTGAGGA ATGCACAGTG
 430 440 450 460 470 480
 TTTCCCTGTT TATCCATCCC CTGCAAACCTG CAGAGTGGCA CTCATTGCTT GTGGACGGAC
 490 500 510 520 530 540
 CAGCTCCTCC AAGGCTCTGA AAAGGGCTTC CAGTCCCGTC ACCTTGCCCTG CCTGCCTCGG
 550 560 570 580 590 600
 GAGCCAGGGC TGTGCACCTG GCAGTCCCTG CGGTCCCAGA TAGCCTGAAT CCTGCCCGGA
 610 620 630 640 650 660
 GTGGAAGCTG AAGCCTGCAC AGTGTCCACC CTGTTCCCAC TCCCATCTTT CTTCCGGACA
 670 680 690 700
 ATGAAATAAA GAGTTACCAC CCAGCAAAAA AAAAAAGGAA TTC--

Please replace the paragraph [018], with the following paragraph:

--[018] A second preferred DNA sequence has been discovered which has an additional nucleotide sequence 5' to the initiator sequence. This sequence, which contains as the eighty-second through four-hundred-thirty-second nucleotides nucleotides 1 through 351 of the first preferred sequence set forth above, has the following nucleotide sequence (SEQ ID No: 6):

10 20 30 40 50 60
 GGCCATCGCC GCAGATCCAG CGCCCAGAGA GACACCAGAG AACCCACCAT GGCCCCCTTT

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70 80 90 100 110 120
GACCCCTGGC TTCTGCATCC TGTTGTTGCT GTGGCTGATA GCCCCAGCAG GGCCTGCACC
130 140 150 160 170 180
TGTGTCCCAC CCCACCCACA GACGGCCTTC TGCAATTCCG ACCTCGTCAT CAGGGCCAAG
190 200 210 220 230 240
TTCGTGGGGA CACCAGAAGT CAACCAGACC ACCTTATACC AGCGTTATGA GATCAAGATG
250 260 270 280 290 300
ACCAAGATGT ATAAAGGGTT CCAAGCCTTA GGGGATGCCG CTGACATCCG GTTCGTCTAC
310 320 330 340 350 360
ACCCCCGCCA TGGAGAGTGT CTGGGGATAC TTCCACAGGT CCCACAACCG CAGCGAGGAG
370 380 390 400 410 420
TTTCTCATTG CTGGAAAAC TGCAGGATGGA CTCTTGCACA TCACTACCTG CAGTTTCGTG
430
GCTCCCTGGA AC--

Please replace the paragraph [019], with the following paragraph:

--[019] A third preferred DNA sequence which incorporates the 5' region of the second preferred sequence and the 3' sequence of the first preferred sequence, has the following nucleotide sequence (SEQ ID No: 7):

10 20 30 40 50 60
GGCCATCGCC GCAGATCCAG CGCCCAGAGA GACACCAGAG AACCCACCAT GGCCCCCTTT
70 80 90 100 110 120
GACCCCTGGC TTCTGCATCC TGTTGTTGCT GTGGCTGATA GCCCCAGCAG GGCCTGCACC
130 140 150 160 170 180
TGTGTCCCAC CCCACCCACA GACGGCCTTC TGCAATTCCG ACCTCGTCAT CAGGGCCAAG
190 200 210 220 230 240
TTCGTGGGGA CACCAGAAGT CAACCAGACC ACCTTATACC AGCGTTATGA GATCAAGATG
250 260 270 280 290 300
ACCAAGATGT ATAAAGGGTT CCAAGCCTTA GGGGATGCCG CTGACATCCG GTTCGTCTAC
310 320 330 340 350 360
ACCCCCGCCA TGGAGAGTGT CTGGGGATAC TTCCACAGGT CCCACAACCG CAGCGAGGAG
370 380 390 400 410 420
TTTCTCATTG CTGGAAAAC TGCAGGATGGA CTCTTGCACA TCACTACCTG CAGTTTCGTG

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C3
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430	440	450	460	470	480
GCTCCCTGGA	ACAGCCTGAG	CTTAGCTCAG	CGCCGGGGCT	TCACCAAGAC	CTACACTGTT
490	500	510	520	530	540
GGCTGTGAGG	AATGCACAGT	GTTTCCCTGT	TTATCCATCC	CCTGCAAACCT	GCAGAGTGGC
550	560	570	580	590	600
ACTCATTGCT	TGTGGACGGA	CCAGCTCCTC	CAAGGCTCTG	AAAAGGGGCTT	CCAGTCCCGT
610	620	630	640	650	660
CACCTTGCCT	GCCTGCCTCG	GGAGCCAGGG	CTGTGCACCT	GGCAGTCCCT	GCGGTCCCAG
670	680	690	700	710	720
ATAGCCTGAA	TCCTGCCCCG	AGTGGAAGCT	GAAGCCTGCA	CAGTGTCCAC	CCTGTTCCCA
730	740	750	760	770	780
CTCCCATCTT	TCTTCCGGAC	AATGAAATAA	AGAGTTACCA	CCCAGCAAAA	AAAAAAAGGA--

Please replace the paragraph [030] with the following paragraph:

--[030] A first preferred portable DNA sequence of the present invention has a nucleotide sequence SEQ ID No: 5 as follows:

C4

10	20	30	40	50	60
GTTGTTGCTG	TGGCTGATAG	CCCCAGCAGG	GCCTGCACCT	GTGTCCCACC	CCACCCACAG
70	80	90	100	110	120
ACGGCCTTCT	GCAATTCCGA	CCTCGTCATC	AGGGCCAAGT	TCGTGGGGAC	ACCAGAAGTC
130	140	150	160	170	180
AACCAGACCA	CCTTATACCA	GCGTTATGAG	ATCAAGATGA	CCAAGATGTA	TAAAGGGTTC
190	200	210	220	230	240
CAAGCCTTAG	GGGATGCCGC	TGACATCCGG	TTCGTCTACA	CCCCCGCCAT	GGAGAGTGTC
250	260	270	280	290	300
TGCGGATACT	TCCACAGGTC	CCACAACCGC	AGCGAGGAGT	TTCTCATTCG	TGGAAAACCTG
310	320	330	340	350	360
CAGGATGGAC	TCTTGACAT	CACTACCTGC	AGTTTCGTGG	CTCCCTGGAA	CAGCCTGAGC
370	380	390	400	410	420
TTAGCTCAGC	GCCGGGGCTT	CACCAAGACC	TACACTGTTG	GCTGTGAGGA	ATGCACAGTG
430	440	450	460	470	480
TTTCCCTGTT	TATCCATCCC	CTGCAAACCTG	CAGAGTGGCA	CTCATTGCTT	GTGGACGGAC
490	500	510	520	530	540
CAGCTCCTCC	AAGGCTCTGA	AAAGGGCTTC	CAGTCCCGTC	ACCTTGCCCTG	CCTGCCTCGG

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550 560 570 580 590 600
 GAGCCAGGGC TGTGCACCTG GCAGTCCCTG CGGTCCCAGA TAGCCTGAAT CCTGCCCGGA
 610 620 630 640 650 660
 GTGGAAGCTG AAGCCTGCAC AGTGTCCACC CTGTTCCCAC TCCCATCTTT CTTCCGGACA
 670 680 690 700
 ATGAAATAAA GAGTTACCAC CCAGCAAAAA AAAAAAGGAA TTC--

Please insert after [030], the following new paragraph:

--[030A] The first preferred portable DNA sequence encodes a metalloproteinase inhibitor having, as a mature protein, the amino acid sequence SEQ ID No: 1 of Table 1 (using the three letter abbreviations for amino acids). The amino acid at position +1 is cysteine (Cys). The amino acid at position +184 is alanine (Ala). As seen in the other preferred portable DNA sequences described below, the DNA sequence encoding a metalloproteinase inhibitor may also encode leader sequences. The leader sequences may be designated by negative numbers beginning with -1.

TABLE 1

	+1	
	Cys Thr Cys Val Pro Pro His Pro Gln	9
Thr Ala Phe Cys Asn Ser Asp Leu Val Ile Arg Ala Lys Phe Val Gly Thr Pro Glu Val		29
Asn Gln Thr Thr Leu Tyr Gln Arg Tyr Glu Ile Lys Met Thr Lys Met Tyr Lys Gly Phe		49
Gln Ala Leu Gly Asp Ala Ala Asp Ile Arg Phe Val Tyr Thr Pro Ala Met Glu Ser Val		69
Cys Gly Tyr Phe His Arg Ser His Asn Arg Ser Glu Glu Phe Leu Ile Ala Gly Lys Leu		89
Gln Asp Gly Leu Leu His Ile Thr Thr Cys Ser Phe Val Ala Pro Trp Asn Ser Leu Ser		109
Leu Ala Gln Arg Arg Gly Phe Thr Lys Thr Tyr Thr Val Gly Cys Glu Glu Cys Thr Val		129
Phe Pro Cys Leu Ser Ile Pro Cys Lys Leu Gln Ser Gly Thr His Cys Leu Trp Thr Asp		149
Gln Leu Leu Gln Gly Ser Glu Lys Gly Phe Gln Ser Arg His Leu Ala Cys Leu Pro Arg		169
Glu Pro Gly Leu Cys Thr Trp Gln Ser Leu Arg Ser Gln Ile Ala		

+184 SEQ ID NO: 1--

Please replace paragraph [031], with the following paragraph:

--[031] A second preferred portable DNA sequence of the present invention has the following nucleotide sequence (SEQ ID No: 6):

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10 20 30 40 50 60
 GGCCATCGCC GCAGATCCAG CGCCCAGAGA GACACCAGAG AACCCACCAT GGCCCCCTTT
 70 80 90 100 110 120
 GACCCCTGGC TTCTGCATCC TGTGTGTTGCT GTGGCTGATA GCCCCAGCAG GGCCTGCACC
 130 140 150 160 170 180
 TGTGTCCCAC CCCACCCACA GACGGCCTTC TGCAATTCCG ACCTCGTCAT CAGGGCCAAG
 190 200 210 220 230 240
 TTCGTGGGGA CACCAGAACT CAACCAGACC ACCTTATACC AGCGTTATGA GATCAAGATG
 250 260 270 280 290 300
 ACCAAGATGT ATAAAGGGTT CCAAGCCTTA GGGGATGCCG CTGACATCCG GTTCGTCTAC
 310 320 330 340 350 360
 ACCCCCCGCA TGGAGAGTGT CTGCGGATAC TTCCACAGGT CCCACAACCG CAGCGAGGAG
 370 380 390 400 410 420
 TTTCTCATTT CTGGAAAACG GCAGGATGGA CTCTTGACAC TCACTACCTG CAGTTTCGTG
 430
 GCTCCCTGGA AC--

Please replace paragraph [033], with the following paragraph:

--[033] A third preferred portable DNA sequence has the nucleotide sequence (SEQ ID No: 7):

10 20 30 40 50 60
 GGCCATCGCC GCAGATCCAG CGCCCAGAGA GACACCAGAG AACCCACCAT GGCCCCCTTT
 70 80 90 100 110 120
 GACCCCTGGC TTCTGCATCC TGTGTGTTGCT GTGGCTGATA GCCCCAGCAG GGCCTGCACC
 130 140 150 160 170 180
 TGTGTCCCAC CCCACCCACA GACGGCCTTC TGCAATTCCG ACCTCGTCAT CAGGGCCAAG
 190 200 210 220 230 240
 TTCGTGGGGA CACCAGAACT CAACCAGACC ACCTTATACC AGCGTTATGA GATCAAGATG
 250 260 270 280 290 300
 ACCAAGATGT ATAAAGGGTT CCAAGCCTTA GGGGATGCCG CTGACATCCG GTTCGTCTAC
 310 320 330 340 350 360
 ACCCCCCGCA TGGAGAGTGT CTGCGGATAC TTCCACAGGT CCCACAACCG CAGCGAGGAG
 370 380 390 400 410 420
 TTTCTCATTT CTGGAAAACG GCAGGATGGA CTCTTGACAC TCACTACCTG CAGTTTCGTG

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430 440 450 460 470 480
 GCTCCCTGGA ACAGCCTGAG CTTAGCTCAG CGCCGGGGCT TCACCAAGAC CTACACTGTT
 490 500 510 520 530 540
 GGCTGTGAGG AATGCACAGT GTTTCCTGT TTATCCATCC CCTGCAAACCT GCAGAGTGGC
 550 560 570 580 590 600
 ACTCATTGCT TGTGGACGGA CCAGCTCCTC CAAGGCTCTG AAAAGGGGCTT CCAGTCCCGT
 610 620 630 640 650 660
 CACCTTGCCT GCCTGCCTCG GGAGCCAGGG CTGTGCACCT GGCAGTCCCT GCGGTCCCAG
 670 680 690 700 710 720
 ATAGCCTGAA TCCTGCCCCGG AGTGGAAGCT GAAGCCTGCA CAGTGTCCAC CCTGTTCCCA
 730 740 750 760 770 780
 CTCCCATCTT TCTTCCGGAC AATGAAATAA AGAGTTACCA CCCAGCAAAA AAAAAAAGGA--

C7
Cond

Please paragraph [059], with the paragraph:

--[059] It is anticipated that translation of mRNA coding for the metalloproteinase inhibitor in yeast will be more efficient with the preferred codon usage of yeast than with the sequence present in pUC8-Fic, as identified in Example 2, which has been tailored to the prokaryotic bias. For this reason, the portion of the 5' end of the portable DNA sequence beginning at the *Tth111I* site is preferably resynthesized. The new sequence favors the codons most frequently used in yeast. This new sequence preferably has the following nucleotide sequence:

C8

HgiAI
 (SEQ ID No: 8) 5' GAT CCG TGC ACT TGT GTT CCA CCA CAC
 (SEQ ID No: 9) GC ACG TGA ACA CAA GGT GGT GTG

CCA CAA ACT GCT TTC TGT AAC TCT GAC C
 GGT GTT TGA CGA AAG ACA TTG AGA CTG GA 3'--

Please replace paragraph [075], with the following paragraph:

--[075] In this method, the portable DNA sequences are those synthetic or naturally-occurring polynucleotides described above. In a preferred embodiment of the

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present method, the portable DNA sequence has the nucleotide sequence SEQ ID No:
5 as follows:

10 20 30 40 50 60
GTTGTTGCTG TGGCTGATAG CCCCAGCAGG GCCTGCACCT GTGTCCCACC CCACCCACAG

70 80 90 100 110 120
ACGGCCTTCT GCAATTCCGA CCTCGTCATC AGGGCCAAGT TCGTGGGGAC ACCAGAAGTC

130 140 150 160 170 180
AACCAGACCA CTTTATACCA GCGTTATGAG ATCAAGATGA CCAAGATGTA TAAAGGGTTC

190 200 210 220 230 240
CAAGCCTTAG GGGATGCCGC TGACATCCGG TTCGTCTACA CCCCCGCCAT GGAGAGTGTG

250 260 270 280 290 300
TGCGGATACT TCCACAGGTC CCACAACCGC AGCGAGGAGT TTCTCATTGC TGGAAAAC TG

310 320 330 340 350 360
CAGGATGGAC TCTTGCACAT CACTACCTGC AGTTTCGTGG CTCCCTGGAA CAGCCTGAGC

370 380 390 400 410 420
TTAGCTCAGC GCCGGGGCTT CACCAAGACC TACACTGTTG GCTGTGAGGA ATGCACAGTG

430 440 450 460 470 480
TTTCCCTGTT TATCCATCCC CTGCAAACTG CAGAGTGGCA CTCATTGCTT GTGGACGGAC

490 500 510 520 530 540
CAGCTCCTCC AAGGCTCTGA AAAGGGCTTC CAGTCCCGTC ACCTTGCTTG CCTGCCTCGG

550 560 570 580 590 600
GAGCCAGGGC TGTGCACCTG GCAGTCCCTG CGGTCCCAGA TAGCCTGAAT CCTGCCC GGA

610 620 630 640 650 660
GTGGAAGCTG AAGCCTGCAC AGTGTCCACC CTGTTCCCAC TCCCATCTTT CTTCCGGACA

670 680 690 700
ATGAAATAAA GAGTTACCAC CCAGCAAAAA AAAAAAGGAA TTC--

Please replace paragraph [084], with the following paragraph:

--[084] In certain circumstances, the metalloproteinase inhibitor will assume its proper, active structure upon expression in the host microorganism and transport of the protein through the cell wall or membrane into the periplasmic space. This will generally occur if DNA coding for an appropriate leader sequence has been linked to the DNA

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C10
cont

coding for the recombinant protein. The preferred metalloproteinase inhibitors of the present invention will assume their mature, active form upon translocation out of the inner cell membrane. The structures of numerous signal peptides have been published, for example by Marion E.E. Watson in Nuc. Acid Res. 12: 5145-5164, 1984, specifically incorporated herein by reference. It is intended that these leader sequences, together with portable DNA, will direct intracellular production of a fusion protein which will be transported through the cell membrane and will have the leader sequence portion cleaved upon release from the cell.--

Please replace paragraph [0104], with the following paragraph:

C11

--[0104] The structure of FIBAC A is

(SEQ ID No: 10) GA TCC GCG ATC GGA GTG TAA GAA ATG TGC ACT
(SEQ ID No: 11) G CGC TAG CCT CAC ATT CTT TAC ACG TGA

TGC GTT CCG CCG CAT CCG CAG ACT GCT TTC
ACG CAA GGC GGC GTA GGC GTC TGA CGA AAG

TGC AAC TCT GAC C
ACG TTG AGA CTG GA--

Please replace paragraph [0106], with the following paragraph:

C12

--[0106] Component oligonucleotide FA1 (SEQ ID No: 12) is:
GATCC GCGAT CGGAG TGTA GAAAT GTGCA CTTGC--

Please replace paragraph [0107], with the following paragraph:

C13

--[0107] Component oligonucleotide FA2 (SEQ ID No: 13) is:
GGAACG CAAGT GCACA TTTCT TACAC TCCGA TCGCG--

Please replace paragraph [0108], with the following paragraph:

C14

--[0108] Component oligonucleotide FA3 (SEQ ID No: 14) is:
GTTT CGCCG CATCC GCAGA CTGCT TTCTG CAACT CTGAC C--

Please replace paragraph [0109], with the following paragraph:

C15

--[0109] Component oligonucleotide FA4 (SEQ ID No: 15) is:
AGGTC AGAGT TGCAG AAAGC AGTCT GCGGA TGCGG C--

Please replace paragraph [0112], with the following paragraph:

C16

--[0112] Linker A1 (SEQ ID No: 16) is: AATTGGCAG--

Please replace paragraph [0113], with the following paragraph:

C17

--[0113] Linker A2 (SEQ ID No: 17) is: TCGACTGCC--

Please replace paragraph [0116], with the following paragraph:

--[0116] The sequence of the sense strand (SEQ ID No: 18) is:

10	20	30	40	50	60
GAATTCGATA	TCTCGTTGGA	GATATTCATG	ACGTATTTTG	GATGATAACG	AGGCGCAAAA
E T E			F	M	H
C A C			O	N	H
O Q O			K	L	A
1 1 5			1	1	1

70	80	90	100	110
AATGAAAAAG	ACAGCTATCG	CGATCGCAGT	GGCACTGGCT	GGTTTCGCTA
	A	NF	PS	
	L	RN	VA	
	U	UU	UU	
	1	12	1A	

120	130
GCGCA	GGCCTCTGGT
H S H M	HA
H T A N	IL
A U E L	NU
1 1 3 1	31--

C18

Please replace paragraph [0120], with the following paragraph:

C19

--[0120] Linker B1 (SEQ ID No: 19) is: GATCCCAGGCCTGCA--

Please replace paragraph [0121], with the following paragraph::

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C20

--[0121] Linker B2 (SEQ ID No: 20) is: GGCCTGG--

Please replace paragraph [0136], with the following paragraph:

C21

--[0136] The second preferred sequence (SEQ ID No: 6) as set forth herein, i.e.,

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 GGCCATCGCC GCAGATCCAG CGCCCAGAGA GACACCAGAG AACCCACCAT GGCCCCCTTT
 70 80 90 100 110 120
 GACCCCTGGC TTCTGCATCC TGTTGTTGCT GTGGCTGATA GCCCCAGCAG GGCCTGCACC
 130 140 150 160 170 180
 TGTGTCCCAC CCCACCCACA GACGGCCTTC TGCAATTCCG ACCTCGTCAT CAGGGCCAAG
 190 200 210 220 230 240
 TTCGTGGGGA CACCAGAAGT CAACCAGACC ACCTTATACC AGCGTTATGA GATCAAGATG
 250 260 270 280 290 300
 ACCAAGATGT ATAAAGGGTT CCAAGCCTTA GGGGATGCCG CTGACATCCG GTTCGTCTAC
 310 320 330 340 350 360
 ACCCCCCGCA TGGAGAGTGT CTGCGGATAC TTCCACAGGT CCCACAACCG CAGCGAGGAG
 370 380 390 400 410 420
 TTTCTCATTT CTGGAAACT GCAGGATGGA CTCTTGACAC TCACTACCTG CAGTTTCGTG
 430
 GCTCCCTGGA AC--

IN THE CLAIMS:

Please cancel claim 26 without prejudice or disclaimer. Please amend claim 25, as follows:

25. (Amended) A purified collagenase inhibitor protein, said protein consisting essentially of an amino acid sequence selected from among the following:

- a) amino acid sequence SEQ ID NO: 2; or
- b) the amino acid sequence of a) or of SEQ ID NO: 1, further having a Met at position -1; or
- c) the amino acid sequence of a) or of SEQ ID NO: 1, further having a leader sequence at the N-terminal, -1 position, wherein said leader sequence consists essentially of the following amino acid sequence from positions -38 to -1:

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